Progress in the management of CKD in patients with type 2 diabetes: How might non-steroidal MRAs change the treatment paradigm?

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Expert panel

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Agenda

Why does the treatment landscape for patients with T2D and CKD still require novel therapies?

Why are non-steroidal MRAs being investigated in patients with T2D and CKD and what do the latest data show?

How might non-steroidal MRAs address unmet needs in T2D and CKD and fit into the current treatment paradigm?

CKD, chronic kidney disease; MRA, mineralocorticoid receptor antagonist; T2D, type 2 diabetes.

Comprehensive T2D and CKD management to reduce risks of kidney disease progression and CVD

KDIGO guideline recommendations

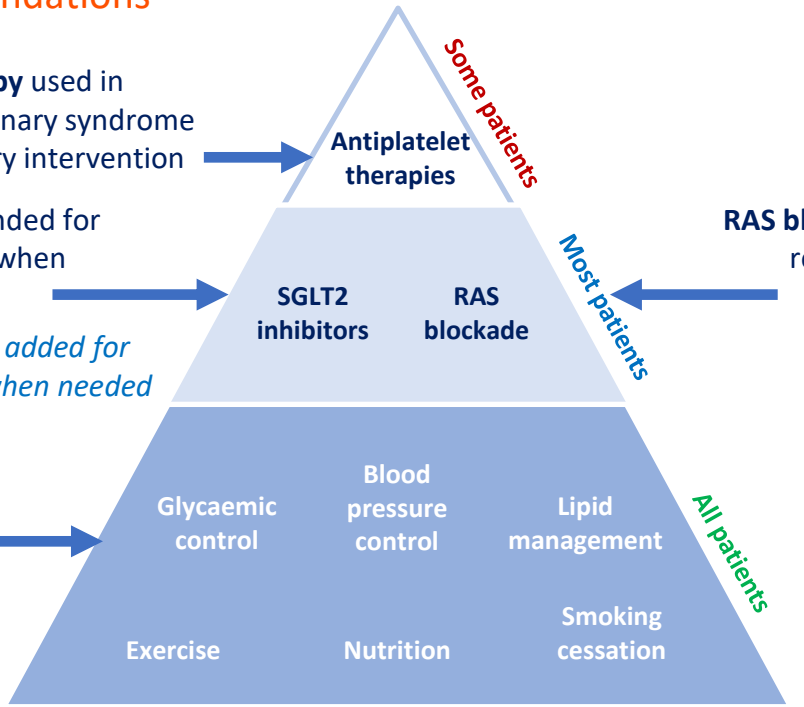
Dual anti-platelet therapy used in patients after acute coronary syndrome or percutaneous coronary intervention

SGLT2 inhibitors recommended for patients with T2D and CKD when **eGFR ≥30 mL/min/1.73 m²**

***GLP-1 RAs** may be added for glycemic control when needed*

Glycaemic control based on combination of **metformin** and **SGLT2 inhibitors** for T2D

RAS blockade (ACE inhibitor or ARB) recommended for patients with albuminuria and hypertension

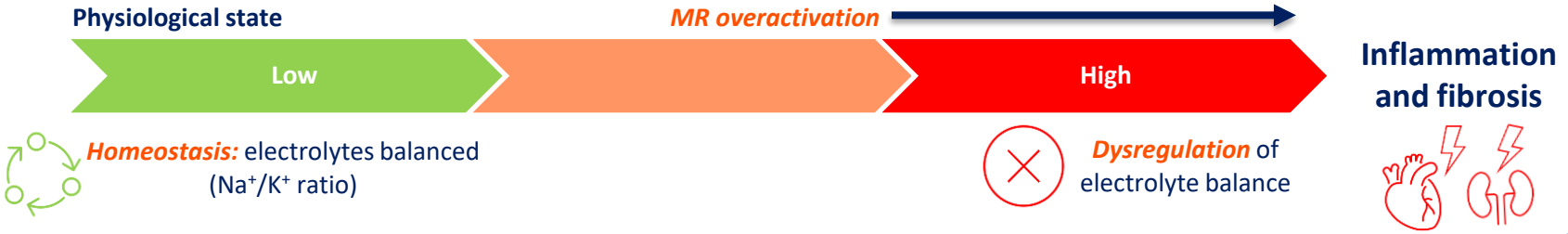


ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; RAS, renin-angiotensin system; SGLT2, sodium–glucose cotransporter-2; T2D, type 2 diabetes.

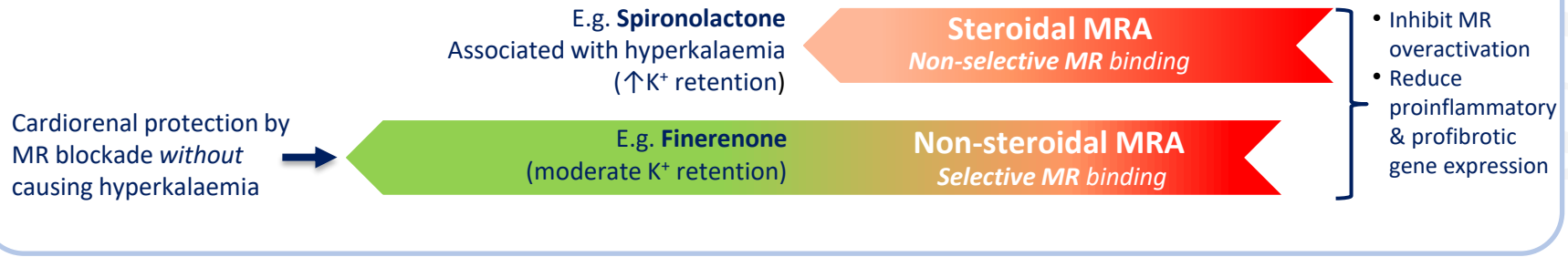
Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. *Kidney Int.* 2020;98(Suppl. 4):S1–S115.

Rationale for blockade of MR in patients with T2D and CKD

- MR gene expression controls fluid, electrolyte and haemodynamic homeostasis
- Overactivation of the MR causes inflammation and fibrosis that damages the kidney and heart



Blockade of the MR aims to slow progression of CKD



CKD, chronic kidney disease; MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonist; K+, potassium; Na+, sodium; T2D, type 2 diabetes.

Agarwal R, et al. *Nephrol Dial Transplant*. 2020; doi:10.1093/ndt/gfaa294.

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CV and renal outcome trials in patients with T2D and CKD

	FIDELIO-DKD[1]	FIGARO-DKD[2,3]	DAPA-CKD[4]	CREDENCE[5]
Treatment	**Finerenone** or PBO	**Finerenone** or PBO	**Dapagliflozin** or PBO	**Canagliflozin** or PBO
Patient population	**N=5,734; CKD + T2D**	**N=7,437; CKD + T2D**	**N=4,304; CKD ± T2D**	**N= 4,401; CKD + T2D ± previous CVD**
UACR (mg/g) **eGFR** (mL/min/1.73 m²)	**UACR** 30–<300 & **eGFR** 25–<60 **or** **UACR** 300–≤5000 & **eGFR** 25–<75	**UACR** 30–<300 & **eGFR** 25–≤90 **or** **UACR** 300–≤5,000 & **eGFR** ≥60	**UACR** 200–≤5,000 & **eGFR** 25–≤75	**UACR** 300–≤5,000 & **eGFR** 30–<90
Primary composite outcome	Onset of kidney failure, sustained ≥40% eGFR decline or renal death **HR 0.82,** p=0.001 vs PBO	Onset of time to CV death, nonfatal MI, nonfatal stroke or HHF **HR 0.87,** p=0.03 vs PBO *Largely driven by 29% redn in HHF*	Sustained ≥50% eGFR decline, ESKD, and renal or CV death **HR 0.61,** p<0.001 vs PBO	ESKD, doubling of sCr, or renal or CV death **HR 0.70**, p=0.00001 vs PBO
Key secondary endpoint(s)	Composite of CV death, nonfatal MI, nonfatal stroke or HHF **HR 0.86,** p=0.03 vs PBO	Composite of onset of kidney failure, sustained ≥40% eGFR decline or renal death **HR 0.87** (p=NS)	Sustained ≥50% eGFR decline, ESKD or renal death **HR 0.56**, p<0.001 vs PBO CV death or HHF **HR 0.71**, p=0.009 vs PBO All-cause mortality **HR 0.69**, p=0.004 vs PBO	CV death or HHF **HR 0.69**, p<0.001 vs PBO CV death, MI or stroke **HR 0.80**, p=0.01 vs PBO HHF **HR 0.61**, p<0.001 vs PBO

CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease, HHF, hospitalization for heart failure; HR, hazard ratio; MI, myocardial infarction; NS, not significant; PBO, placebo; sCr, serum creatinine; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio.

1. Bakris G, et al. *N Engl J Med.* 2020;383:2219–29; 2. Ruilope L, et al. *Am J Nephrol.* 2019;50:345–56; 3. Pitt B, et al. *N Engl J Med.* 2021. DOI: 10.1056/NEJMoa2110956; 4. Heerspink H, et al. *N Engl J Med.* 2020;383:1436–46; 5. Perkovic V, et al. *N Engl J Med.* 2019;380:2295–306.

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FIDELITY: Meta-analysis of FIDELIO-DKD and FIGARO-DKD

To evaluate stage of kidney disease and efficacy of finerenone on composite CV and renal endpoints

Patient population	13,026 patients with CKD + T2D • Treated with RAS blockade • Serum K^+ ≤4.8 mmol/L	Finerenone or PBO
Primary composite outcome	Onset of time to CV death, nonfatal MI, nonfatal stroke or HHF, & its relationship with UACR/eGFR	Follow-up: 3 years **HR 0.86** p=0.0018 vs PBO
Secondary composite outcome	Onset of kidney failure, sustained ≥57% eGFR decline for ≥4 weeks or renal death, & its relationship with UACR/eGFR	**HR 0.77** p=0.0002 vs PBO
Safety outcomes	• Safety outcomes generally similar between treatment arms • Hyperkalaemia: 14.0% with finerenone vs 6.9% with PBO • Treatment discontinuation due to hyperkalaemia was infrequent: 1.7% vs 0.6%	

CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure; HR, hazard ratio; MI, myocardial infarction; PBO, placebo; RAS, renin–angiotensin system; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio.

Filippatos G, Agarwal R. Presented at the ESC Congress 2021. 28 Aug 2021. Available at: www.escardio.org/The-ESC/Press-Office/Press-releases/Finerenone-benefits-patients-with-diabetes-across-spectrum-of-kidney-disease (accessed 4 October 2021).

Subanalysis of FIGARO-DKD: Finerenone effect by baseline SGLT2i use

eGFR status and baseline medication use differed between groups

% Patients at baseline	No SGLT2i (n=6,734)	SGLT2i (n=618)
eGFR <60 mL/min/1.73 m^2	39	29
Statins	69	83
Metformin	68	83
GLP-1 RAs	6.4	19.3

Finerenone had CV and renal benefits independent of, and in combination with, SGLT2is

Finerenone versus PBO	No SGLT2i (n=6,734)	SGLT2i (n=618)	$P_{interaction}$
Change in UACR, %	-32	-41	0.04
CV composite outcome, HR	0.89	0.49	0.11
Renal composite outcome, HR			
≥40% eGFR decrease	0.88	0.70	0.69
≥57% eGFR decrease	0.80	0.51	0.28

CV, cardiovascular; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; PBO, placebo; SGLT2i, sodium–glucose co-transporter 2 inhibitor; UACR, urine albumin-to-creatinine ratio.

McGill J. Presented at the EASD Virtual Meeting 2021. 1 October 2021. Available at: https://virtualcongress.easd.org/program/easd/easd2021/en-GB (accessed 4 October 2021).

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